Health Effects of Metals: A Role for Evolution?

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Metals have been mined and used since ancient times. The industrial era has seen a sharp increase in both the amounts and variety of metals that find applications in industry. The inadvertent release of metals, such as from fossil fuel consumption, also adds to the global burden. A number of catastrophic outbreaks have alerted us to the occupational and environmental health risks. Life on this planet has evolved in the presence of metals. Cells learned to make use of the more abundant metals in the Archean oceans as an integral component in their structure and function. Today, we inherit these as the essential metals. At the same time, evolving life must have developed means of coping with the potentially toxic actions of metals. The appearance of oxygen in the atmosphere in the Precambrian period also resulted in cells both using and developing protective mechanisms against what must have been a highly toxic, reactive gas. Atmospheric oxygen must have increased the solubility of many metals as insoluble metal sulfides were oxidized to the more soluble sulfates. It may be no coincidence that the protective mechanisms for oxygen are also used to protect against a number of toxic metals. Selected examples are given on the role of evolution in metal toxicology, specifically, examples where the normal function of essential metals is deranged by competition with nonessential metals. Examples are also given of protective mechanisms that involve enzymes or cofactors involved in the oxygen defense system. — Environ Health Perspect 103(Suppl 1):9–12 (1995)

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Introduction

Human Exposure to Metals

Since metals are ubiquitous in time and space, humans must always have been exposed to them. The date of the first human use of metals is not known, but it must date back many thousands of years. A lead figurine in the British Museum is dated at 3800 B.C. (Table 1). Mercury, arsenic, silver, and zinc were used in ancient times. Thus, use of copper and tin alloys to form bronze (perhaps also antimony) defines the start of the Bronze Age about 3500 B.C., and the introduction of iron defines the start of the Iron Age in about 1500 B.C.

The pace of discovery of metals picked up dramatically in the 18th century, peaked in the 19th, and finally, in the current century, the remaining metals in the periodic table were discovered (Table 2). In addition, the transuranic metals made their appearance on this planet starting in the 1940s with the advent of nuclear fission.

An example of the global dispersion of a metal due to human use is given in Figure 1. The concentrations of lead in a Greenland ice sheet give a historical record of atmospheric levels of lead. Thus, the lev-

Table 1. The ancient metals: evidence of the human use of metals in ancient times.[a]

Arsenic
Used in Ancient Greece
Lead
Figurine in British Museum dated 3800 B.C.
Mined in Spain, 2000 B.C.
Lead pipes in Roman empire
Mercury
Named quicksilver by Aristotle, 350 B.C.
Silver and gold
Ornaments in royal tombs of Chaldea, 4000 B.C.
Zinc and copper
Romans used brass coins

[a]From Hunter (1).

els of lead rose gradually until this century when an abrupt rise is seen. The timing of the onset of this rise coincides with the introduction of lead as an antiknock additive in motor fuel. The huge quantities of lead used for this purpose and the ensuing emission to the atmosphere in automobile exhaust probably account for this sharp increase in deposition of lead in the snow fields of Greenland.

Information of this type is limited to only a few metals so far. Nevertheless, we can expect increasing use of any metal following its discovery. Today, metals are finding a variety of novel applications. The use of metals in the "silicon valley" industries is an example of the use of relatively rare metals. The new-technology metals include: gallium, arsenic, tellurium, beryllium, germanium, aluminum, cadmium, indium, palladium, molybdenum, gold, niobium, tantalum, and unique combinations of pairs of these metals (4). These metals are often used in novel combinations; for example, GaAs, GaAlAs, and CdTe.

Table 2. Approximate date of the discovery or first known use of metals.[a]

Number of metals	Date, centuries
	B.C.
9	4000–300
	A.D.
1	1450
13	1700–1799
39	1800–1899
13	1900–1993

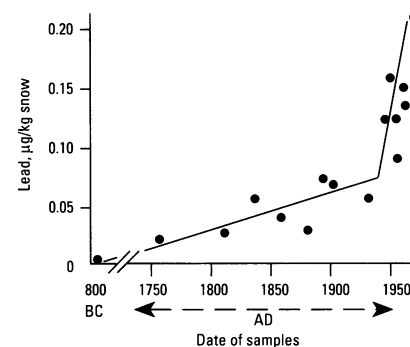[a]Universal Standard Encyclopedia (2).

Figure 1. The levels of lead in cores taken from a Greenland ice sheet are taken to indicate past levels of lead in snow and thereby indicated past atmospheric levels. Adapted from Murozumi et al. (3).

Thus, the current picture of human exposure is one in which not only have the "ancient metals" been well dispersed in our environment but also the variety of metals to which we are occupationally, and ultimately environmentally, exposed is also increasing. Of special concern are those metals that are newly arrived on the exposure scene such as the transuranics

and new combinations of metals in the electronic industries.

A Role of Metals in Evolution

At the very outset of life on this planet, the first cells must have been exposed to many metals and their compounds. The early atmosphere lacked oxygen and could be described as a reducing atmosphere. Many metals should have been present as insoluble sulfides, thus limiting their concentrations in the Archean waters. However, when readily available supplies of hydrogen were exhausted, cyanobacteria first split the water molecule to access the last major reservoir of hydrogen and oxygen was released as a by-product (5).

Although anaerobic cells survive to this day, most cells had to develop protective mechanisms against this new highly toxic gas. In addition, the cell learned to make use of oxygen in respiratory metabolism, thus greatly increasing the efficiency of ATP synthesis. Figure 2 illustrates the role of catalase and superoxide dismutase in protecting the cell against the toxic by-products of oxygen metabolism.

Coincident with the "oxygen storm," metal concentrations in the aqueous environment of these Archean cells must also have risen (7). The insoluble sulfides were oxidized to the soluble sulfates. Mercury vapor, $Hg°$, probably present in the reducing atmosphere at much higher levels than those that exist in today's atmosphere, would be oxidized to the soluble ionic form, Hg^{2+}, and returned to the Earth's surface in rainwater (8). Thus, the cells had to cope not only with an oxygen attack but also an onslaught from numerous metals. The response followed the same general lines; to develop protective mechanisms and to make use of at least some of the metals that today we call the "Essential" metals.
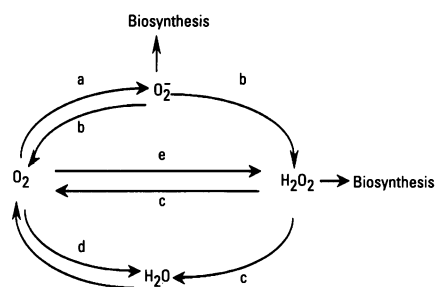
Figure 2. The oxygen cycle adapted from Hill (6). A number of enzymes catalyze the reactions depicted above: a) various enzymes; b) superoxide dismutase; c) catalase; d) cytochrome oxidase; e) various enzymes, e.g., amino acid oxidases.

Figure 3 illustrates a general relationship between the estimated levels of metals in the Archean oceans after the evolution of oxygen. In fact, these levels or their relative concentrations are believed to be similar to current ocean levels. It may be seen that the metals present at higher concentrations became the "essential" metals. Both essential and nonessential metals may be regarded as potentially toxic; for example, chromium and manganese. Nevertheless, defense mechanisms were probably developed. It may be more than just coincidence that the defenses used for oxygen were used for certain metals and that some of the essential metals were used as part of the active site in enzymes used in the oxygen defense system; for example, Fe in catalase and Cu, Mn, and Zn in the dismutases.

The Role of Evolution in the Toxicology of Metals

In considering the role of metals in the early evolution of cells, two important cellular responses should be considered: the cell's incorporation of metals as an essential part of the cell's function and structure, and the protective mechanisms developed as part of the selective process of evolution.

Competition between Essential and Nonessential Metals

From the theoretical point of view, interactions may occur between essential and nonessential metals that have similar chemical properties; for example, the ionic and hydrated radii of the monovalent cations potassium and thallium are closely similar. This explains why thallium is transported into the cells as if it were potassium (11). However, once inside the cell, thallium exerts its toxic effect, perhaps because it cannot mimic potassium in all its functions in the cell.

Lead and calcium ions are sufficiently similar that some degree of both competition and mimicry occurs. In fact, lead mimicry of calcium has been invoked to explain some of the toxic effects of lead on the nervous system (Figure 4). Lead has been shown to compete with calcium for entry into the synaptosome in *in vitro* experiments (12). Once inside the cells, calcium activates a number of kinases, including protein kinase C. This in turn results in phosphorylation of other proteins in the cytoplasm including synapsin, leading to the release of the neurotransmitter, acetylcholine. Recent *in vitro* studies have shown that picomolar concentrations of lead can activate protein kinase C (13). It has been suggested that prolonged stimulation of this
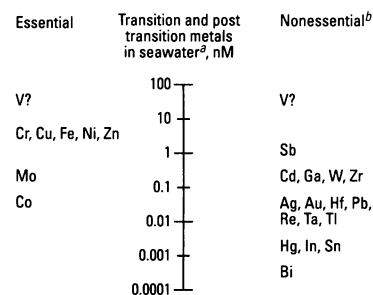
Figure 3. The concentrations of metals in seawater are taken to indicate at least the relative levels of metals in the archean oceans after atmospheric oxygen evolution. Adapted from Egami (9) with data from Libes (10). [a]Data not available for Tc, Rh, Ru, Os, Ir, Pd, Pt, and Po. [b]The nonessential metals are those metals for which evidence is lacking that they are essential. It is possible that an essential role may still be found for some of these metals.

"second messenger" enzyme by lead would produce excessive release of neurotransmitters and deleteriously affect the developing brain (14).

The formation of oxyanions by metals probably dates back to the era of the "oxygen storm". The oxyanions of a number of toxic metals have similar structures to essential oxyanions (Figure 5). Thus, both arsenate and vanadate can mimic phosphate to a certain extent. Arsenate mimics phosphate in the early steps of ATP synthesis but finally forms an unstable arsenate-containing intermediate (16). This "arsenolysis reaction" effectively uncouples ATP synthesis. The fact that arsenate can affect a reaction common to almost all cell types may account for the broad number of cells and tissues poisoned by arsenic.

Hexavalent chromium, in the form of the oxyanion, gains entrance to the cell on the sulfate carrier. Once inside the cell, the chromate oxyanion undergoes reduction, with the production of highly reactive toxic intermediates believed to be ultimately responsible for the carcinogenic action of hexavalent chromium (17).
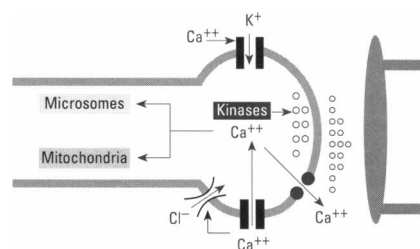
Figure 4. A diagrammatic representation of a neural synapse indicating some of the transport and metabolic reactions that involve ionic calcium.
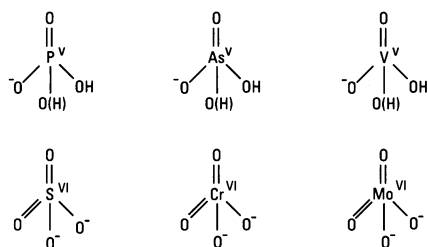
Figure 5. The structures of essential and nonessential oxyanions. Competitive interactions occur within each group of mono (upper row) and divalent (lower row) oxyanions. Adapted from Wetterhahn-Jennette (15).
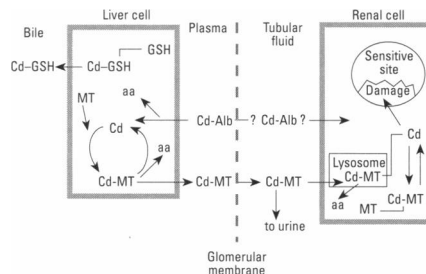

Figure 6. A diagrammatic representation of the protective role of metallothionine against renal cadmium poisoning. Adapted from Nordberg (18).
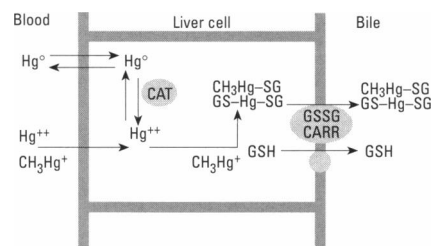

Figure 7. A diagrammatic representation of the removal of both mercury vapor, $Hg°$, divalent mercury, Hg^{2+} and CH_3Hg^+ from the bloodstream and secretion into bile.

A Role for the Oxygen Defense System

Metallothionine is a low molecular weight protein that contains a high proportion of cysteine residues, constituting approximately one-third of all the amino acids in the protein. It also probably evolved as part of the oxygen defenses, as its numerous SH groups make it an effective scavenger of oxidizing free radicals. Its synthesis is induced by a number of toxic metals including cadmium. Metallothionine is believed to defend the kidney from cadmium (Figure 6). Cadmium is transported into the liver after absorption from the diet. In the liver it induces the synthesis of metallothionine and forms a tight complex with this protein. The latter is able to leave the liver, enter the general circulation and pass into the kidney via glomerular filtration and absorption into the proximal tubular cells. Once inside the cells, the metallothionine complex is broken down in the lysosomes, liberating free cadmium. This in turn can induce and bind to metallothionine. This system serves to protect the kidney cells from damage.

However, if the exposure to cadmium rises above a threshold level, the rate of supply of the cadmium metallothionine complex and its subsequent liberation of free cadmium overwhelms the defenses in the kidney cells. In particular, the rate of release of free cadmium exceeds the ability of the cell to synthesize metallothionine and cadmium diverts to sensitive sites.

Glutathione is a unique tripeptide that occurs in a high concentration (millimolar) in most mammalian cells. The SH group of one of its constituent amino acids, cysteine, allows this molecule to provide a reducing redox potential inside the cells and thereby to contribute to the oxygen defense system. The SH group also gives the molecule a high affinity for many metal cations. Indeed, glutathione is known to protect cells against the toxicity of several toxic metals [for a recent review, see Ballatori, (19)].

An example of the role of glutathione in the elimination of mercury from the body is given in Figure 7. Mercury, in the form of inhaled mercury vapor, divalent inorganic mercury, or methylmercury enters the liver cell from the bloodstream. Mercury vapor rapidly crosses cell membranes due to its high lipid solubility (20). The mechanism of entry of the divalent mercury is not well understood but may involve SH-containing carriers (21). Once inside the cell, mercury vapor is oxidized to Hg^{2+} by catalase—using hydrogen peroxide as the oxidant. Both Hg^{2+} and CH_3Hg^+ form a complex with glutathione and are transported out of the cells into bile on the carriers for glutathione conjugates (22,23). This mechanism of protection probably applies to other mammalian cells. For example, Miura et al. (24) have shown that cells resistant to methylmercury have elevated glutathione levels and export methylmercury more rapidly that nonresistant cells. Thus, in the case of mercury compounds, glutathione plays a dual protective role: it combines with metal inside the cell thus protecting sensitive sites and it acts as a means of removal from the cells.

Conclusions

Exposure of humans to trace metals is increasing in terms of the environment levels and in terms of the variety of metals. Life, having evolved on this planet, has developed protective mechanisms. At least some of these mechanisms include enzymes and cofactors involved in the oxygen defense system, perhaps because the appearance of oxygen in the planet's atmosphere also led to the oxidation of metals and conversion to more soluble forms. Given that such defense mechanisms may have evolved over very long time periods, it is of special concern that humans are now being exposed to metals that were previously of very low abundance in the earth's crust and to the transuranics introduced a mere 50 years ago.

The first cells on this planet also evolved mechanisms to make use of metals as integral parts of their structure and function, metals that we now recognize as the "essential" metals. Nonessential toxic metals may compete with essential metals having similar chemical properties. At low levels of the competing metals, the essential metal will "win" in the competition for binding sites. However, as levels of the nonessential metals rise, it will begin to interfere with the normal function of the essential metals. Thus, the essential metals have a capacity to protect the cells against low levels of metal contaminants, but at higher levels the protection fails. Interference with the normal function of the essential metal results in a toxic outcome.

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